

**REMARKS**

Claims 55 – 65, 67, 71, 77 – 79, 81 – 83, 85, 87 – 91 and 103 – 105 are pending in the application. Claims 1 – 54, 63, 66, 68 – 70, 72 – 78, 80, 82, 84, 86, 88, 92 – 102 have been cancelled. Claims 55, 60, and 89 – 91 have been amended. No new claims have been added. No new matter has been added by virtue of the amendments and claims, support being found throughout the specification and claims as originally filed.

Support for the amendment to claims 55 and 60 can be found in the specification, for example at paragraph [0204] – [0208].

Any cancellation of the claims should in no way be construed as acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s).

**Claim Rejections Withdrawn**

The Examiner has withdrawn the rejection of claims 55, 57 – 59, 67 and 71 under 35 USC 102(b) as being anticipated by Dollegast (US 5,078,164).

The Examiner has withdrawn the rejection of claims 55, 57 – 59, 67 and 71 under 35 USC 102(b) as being anticipated by Peeters et al. (US 6,123,819).

**Claim Rejections****35 USC 112, Second Paragraph**

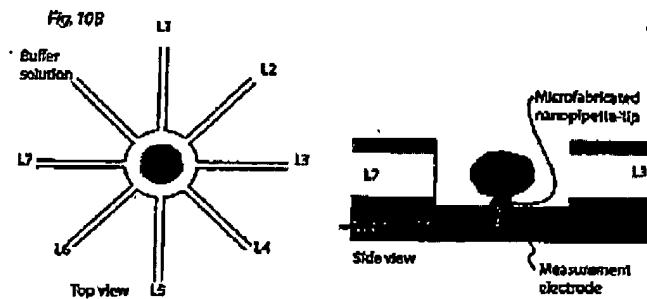
The Examiner has rejected claims 55 – 62, 64, 65, 67, 71, 79, 81 – 83, 85, 87 – 91 and 103 – 105 under 35 USC 112, second paragraph for alleged indefiniteness. Applicants respectfully traverse the rejection.

The Examiner argues that "claims 55 and 60 are still confusing and ambiguous in their recitation of the claimed microfluidics system, and the structure of the claimed

apparatus still cannot be understood, rendering the meaning of the claims unclear." (Office Action, p.2). The Examiner argues that "the substrate comprises a measurement chamber and a raised aperture (and) the raised aperture comprises a tip, and the tip comprises a housing. The measurement chamber comprises a microchannel. But, the relationship of these parts is unclear." (Office Action, p.3). The Examiner argues that "the structure and how the claimed apparatus is used are unclear." (Office Action, p.3). Applicants respectfully disagree.

The instant claims recite a microfluidic system comprising a substrate, wherein the substrate comprises at least one measurement chamber for containing one or more cells or lipid based cell structures, the measurement chamber comprising at least one raised aperture for detecting an electrical property of one or more cells or lipid based cell structures, each aperture comprising a tip, the tip comprising a housing defining a lumen, wherein at least one tip is inserted into a cell or lipid based cell structure, and wherein the substrate further comprises at least one microchannel with at least one inlet and at least one outlet which opens into the at least one measurement chamber, and wherein the at least one microchannel delivers one or more substantially separate aqueous streams into the measurement chamber.

The structure of the claimed microfluidic system is clear as claimed. Applicants direct the Examiner to Figure 10B, below, which shows an enlarged view of the measurement chamber and the insertion of a nanoelectrode into the cell as it is exposed to solution flow from a microchannel (L7) to clearly illustrate an embodiment of the invention as claimed:



The Examiner argues that "it is not clear if the device is a one piece or two piece structure" and that "the relationship of the aperture, the substrate and the measurement chamber" is unclear." (Office Action, p.2 - 3).

The structure of the claimed device is clear from the description and figures as filed.

The claims clearly recite a device where the elements, i.e., the substrate, the microchannels, the measurement chamber, the aperture are related, such that "**the substrate comprises at least one measurement chamber...the measurement chamber comprising at least one raised aperture**" and where "**the substrate further comprises at least one microchannel with at least one inlet and at least one an outlet which opens into the at least one measurement chamber.**" (see claim 1).

The specification provides description of the claimed device:

the invention provides a microfluidic system comprising a substrate that comprises a measurement chamber for containing one or more cells. A plurality of microchannels are fabricated on the substrate whose outlets intersect with, or feed into, the measurement chamber. Preferably, the system comprises one or more of the nanoelectrode devices described above. (p.47, emphasis added).

The Examiner argues further that "claim 60 recites the same apparatus as claim 55 with the change that the aperture is a plurality of solid electrode tips." (Office Action, p.3).

Claim 60 recites a microfluidic system comprising a substrate, wherein the substrate comprises at least one measurement chamber for containing one or more cells or lipid based cell structures, the measurement chamber comprising a plurality of solid electrode tips for detecting an electrical property of one or more cells or lipid based cell structures, the tips comprising a housing defining a lumen, where the housing comprises a solid state conducting material, wherein at least one tip is inserted into a cell or lipid based cell structure, and wherein the substrate further comprises at least one microchannel with at least one inlet and at least one an outlet which opens into the

at least one measurement chamber, and wherein the at least one microchannel delivers one or more substantially separate aqueous streams into the measurement chamber.

Applicants direct the Examiner to the specification, beginning at page 43, where this aspect of the invention is clearly taught:

Therefore in one aspect, the invention provides a system comprising a substrate that comprises a plurality of measurement chambers (e.g. greater than 10 and preferably 96, 384 or 1536 number of chambers). Each chamber on the substrate is containing one or more cells...In addition each measurement chamber is equipped with at least one nanoelectrode device fabricated on the base of the measurement chamber as described above. Most preferably, each measurement chamber is equipped with multiple (e.g., greater than 6 and preferably greater than 30) nanoelectrodes allowing the registration of several cells in each measurement chamber simultaneously. (emphasis added).

Accordingly, Applicants submit that claim 60 is clear as written.

The Examiner further argues that "claim 90 is confusing because the phrase 'scanning a cell across the aqueous streams from the microchannels' is unclear' (and) it cannot be determined where the cell is in the claimed microfluidics system." (Office Action, p.3). Applicants disagree.

The present claims recite that the substrate further comprises at least one microchannel with at least one inlet and at least one outlet which opens into the at least one measurement chamber, and wherein the at least one microchannel delivers one or more substantially separate aqueous streams into the measurement chamber.

Applicants direct the Examiner to the specification which teaches scanning of a cell across aqueous streams from a microchannel, for example where "scanning can be performed by moving the substrate and/or the object, or, can be mediated by pressure drops applied to the channels." (page 18, line 29 – page 19). For example, as taught in the specification, "a receptor or ion-channel is periodically resensitized by scanning it across a plurality of interdigitating channels providing alternating streams of sample

(containing receptor ligands) and ligand-free buffer solution." (page 32, line 24). In particular, Applicants direct the Examiner to the description of Figure 18 beginning on page 28, that teach how a sensor can be moved in relation to fluid streams.

FIGS. 18A-I are top views of microchannel outlets in relationship to a nanoelectrode-contacted cell, collectively showing different methods by which a nanoelectrode-contacted cell can be moved in relation to the fluid streams. FIGS. (18)8A-C show mechanical scanning of the nanoelectrode-contacted cell across stationary microchannel outlets. FIGS. (18)8D-F show mechanical scanning of microchannel outlets relative to a stationary nanoelectrode-contacted cell. FIGS. (18)8G-I show a method for sweeping fluid streams across an immobilized nanoelectrode-contacted cell by controlled variation of the pressure across, and flow rates through, each individual microchannel

In light of the above, Applicants respectfully request that the Examiner withdraw the rejection.

#### **Rejection of Claims Under 35 USC 103(a)**

Claims 55 – 62, 64, 65, 67, 71, 79, 81 – 83, 85, 87 – 91 and 103 - 105 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Maher et al. (US 2002/0025568; the '568 reference herein) and He et al. (US 2003/0049862; the '862 reference herein) in view of Peeters (US 6,123,819; the '819 reference herein) and Hamill et al. (Pflugers Archiv 391: 85 – 100, 1981). Applicants respectfully traverse the rejection.

The claims were set forth above.

The '568 reference is directed to instruments and methods for manipulating membrane potentials of living cells via electrical stimulation. The '568 reference teaches a method of assaying ion channel activity comprising exposing at least one cell to a plurality of electric field pulses so as to create a controlled change in transmembrane potential and activate an ion channel of interest, and detecting ion

channel activity by detecting one or more changes in transmembrane potential without using a patch clamp.

The Examiner argues that the apparatus taught by the '568 reference "comprises a substrate comprising an array of measurement chambers (a microtiter plate) that contains cells. The apparatus comprises an array of microelectrodes that match the wells in the microtiter plate and are arranged in a lid or cover." (Office Action, p.5). As pointed out by the Examiner, the '568 reference uses "two identical, flat electrodes with surfaces that are aligned substantially parallel to each other" within the wells of the microtiter plates (paragraph [0147]). This is shown, for example, in Figure 9, below:

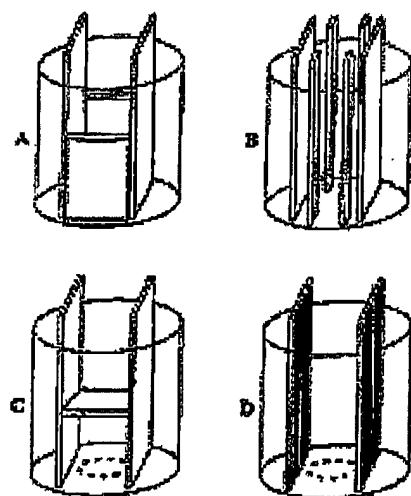


FIG. 9

Figure 1 (A and B), below, exemplifies the apparatus of the '568 invention, and shows the placement of the electrodes in the array. (see, e.g. paragraph [0155]). According to preferred embodiments of the '568 reference the "electrodes typically consist of one or more pairs of electrodes that are arranged in an array that can be retractably moved into, and out of, one or more wells of a multiwell plate." ([0164])

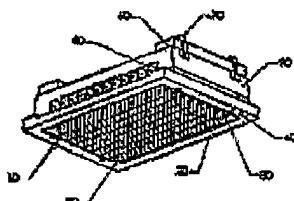


FIG. 1A

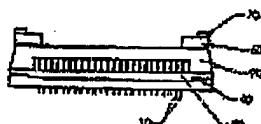


FIG. 1B

The present invention is directed to microfluidic substrates that comprise at least one microchannel with at least one inlet and at least one outlet which opens into the at least one measurement chamber. The microfluidic substrate comprises one or more microchannels which deliver substantially separate aqueous streams into the measurement chamber. Applicants direct the Examiner to the present disclosure, for example at page 56, beginning at line 3, that teaches the delivery of substantially separate streams to the measurement chambers.

The system also can sweep different fluid streams across stationary cells by varying pressure drops across individual microchannels of the substrate. This design is derived from the discovery of a new and unique fluidic behavior; i.e., that lateral interactions and couplings between neighbouring fluid streams as they exit from a set of closely spaced microchannels into a measurement chamber can extend dramatically the distance over which these streams remain collimated. The second design exploits the reversibility of fluid behavior at low Reynold's numbers while the third design is based on the ability to rapidly exchange fluids in microchannels and chambers.

The '568 reference does not teach or suggest a substrate that comprises at least one measurement chamber with at least one raised aperture, where the substrate further comprises at least one microchannel with at least one inlet and at least one an outlet which opens into the at least one measurement chamber, and wherein the at least one microchannel delivers one or more substantially separate aqueous streams into the measurement chamber.

The '862 reference is directed to a microfluidic device that integrates fluidic capability into existing multi-well plates. The '862 reference teaches a device that includes "fluidic modules extending at an angle, preferably orthogonal, from a support structure or plate (and) (e)ach fluidic module is three-dimensional, has a major surface located remotely from the support structure, and at least one sidewall between the major surface and the support structure." ([0007]) There are fluidic channels in each of the fluidic modules.

The Examiner argues that "it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the microtiter plate of Maher et al. with the microfluidics plumbing for microtiter plate lids of He et al., because He discloses that this modification transforms the apparatus into high-throughput apparatus... (m)icrofluidics chips, by comparison, require specialized custom equipment and have much lower throughput." (Office Action, p.6).

The '862 reference does not teach or suggest a substrate that comprises at least one measurement chamber with at least one raised aperture, where the substrate further comprises at least one microchannel with at least one inlet and at least one an outlet which opens into the at least one measurement chamber, and wherein the at least one microchannel delivers one or more substantially separate aqueous streams into the measurement chamber.

It would not even be possible to use the plumbing taught by the '862 reference, where "the arrangement of the fluidic channels in each fluidic module permits one to supply a continuous flow of fresh reagents and solutions into each microplate well (and) ...continuous fluidic movement is useful for such functions as mixing, flow-through washes or filtration" in the system of the '568 reference and arrive at the

present invention, where the substrate comprises at least one microchannel with at least one inlet and at least one outlet which opens into the at least one measurement chamber, and the at least one microchannel delivers one or more substantially separate aqueous streams into the measurement chamber.

Neither the '819 reference nor the Hammil reference cures the defects of the '568 or '862 references. Neither reference, alone or in combination with any of the other cited references, teaches a microfluidic system as claimed.

In particular, the '819 reference does not teach or suggest a microfluidic system as claimed with raised apertures or a plurality of solid electrode tips (e.g., nanotips), where the tips comprise a housing defining a lumen and/or are inserted into a cell or lipid based cell structure. The '811 reference is directed to nanoelectrode arrays that are used for detecting small biological molecules. The '819 reference nowhere teaches tips that comprise a housing defining a lumen and wherein at least one tip is inserted into a cell or lipid based cell structure.

Applicants direct the Examiner to the description of the nanoelectrodes, at column 5, beginning at line 20, where the "(e)lectrodes 26a, 26b and 26c can be formed of a number of materials, either intrinsic or doped, such as gold and platinum and copper and other electrometals." Further, the '819 reference teaches only binding to the electrodes, where "several types of binding or adsorption of the molecule to the nanoelectrode receptor are possible, depending on the chemical composition of the nanoelectrodes, the voltage and the chemical to be measured. Binding forces may include covalent binding, electrostatic binding, hydrogen bonds and van der Waals bonds." (col 6, line 13). Nowhere does the '819 reference suggest any insertion of electrodes into cells, nor would the composition or arrangement of the electrodes facilitate such use.

In light of the above, Applicants respectfully request the withdrawal of the rejection.

**CONCLUSION**

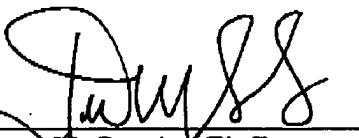
In light of the above remarks, Applicants respectfully request early consideration and allowance of the subject application.

Should the Examiner wish to discuss any of the amendments and/or remarks made herein, the undersigned attorney would appreciate the opportunity to do so.

The Commissioner is hereby authorized to charge any fees that may be required, or credit any overpayment to Deposit Account No. 04-1105.

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Respectfully submitted,

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